

FORM PTO-1500		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371			4121-125 U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 09/857902
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED	
PCT/DE99/03972	8 December 1999	10 December 1998	
TITLE OF INVENTION			
SPERMATOGENESIS PROTEIN			
APPLICANT(S) FOR DO/EO/US			
Zdenek Sedlacek and Annemarie Poustka			
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:			
1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1). 4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date. 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau). b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input checked="" type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)). 7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). (Unsigned) 10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). Items 11. to 16. below concern other document(s) or information included: 11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 14. <input type="checkbox"/> A substitute specification. 15. <input checked="" type="checkbox"/> A small entity statement. <i>Small entity status is claimed.</i> 16. <input type="checkbox"/> Other items or information: EPO Search Report and disk with sequence listings in Patent 2.1.			

NOTE: This application is being filed with an unsigned Oath or Declaration under the provisions of 37 CFR § 1.53 in order that applicants may secure a filing date of June 8, 2001. Upon receipt of a "Notice to File Missing Parts - Filing Date Granted," a executed Declaration and Power of Attorney will be forwarded. The undersigned agent affirmatively states that she has been duly authorized and appointed to file this application on behalf of the applicants and applicants' assignees, and that the Declaration and Power of Attorney to be filed hereafter will confirm the undersigned agent's authorization and appointment. Applicants are considered a small entity and assignee Deutsches Krebsforschungszentrum is also considered a small entity within the meaning of 37 CFR § 1.9.

09/857902

JC03 Rec'd PCT/PTO

08 JUN 2001

- 17.
- ☒
- The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)-(5)):

Search Report has been prepared by the EPO or JPO\$860.00

International preliminary examination fee paid to USPTO (37 CFR 1.482)

.....\$0.00

No International preliminary examination fee paid to USPTO (37 CFR 1.482)

but international search fee paid to USPTO (37 CFR 1.445(a)(2))\$0.00

Neither international preliminary examination fee (37 CFR 1.482) nor

international search fee (37 CFR 1.445(a)(2)) paid to USPTO\$1000.00

International preliminary examination fee paid to USPTO (37 CFR 1.482)

and all claims satisfied provisions of PCT Article 33(2)-(4)\$0.00

ENTER APPROPRIATE BASIC FEE AMOUNT =

CALCULATIONS

PTO USE ONLY

\$ 860.00

Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492(e)).

☐ 20 ☐ 30

\$

Claims

Number Filed

Number Extra

Rate

Total Claims

11-20 =

0

X \$18.00

\$

Independent Claims

1-3 =

0

X \$80.00

\$

Multiple dependent claim(s) (if applicable)

+ \$270.00

\$

TOTAL OF ABOVE CALCULATIONS =

860.00

Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).

\$ 430.00

SUBTOTAL =

\$ 430.00

Processing fee of \$130.00 for furnishing the English translation later than

☐ 20 ☐ 30

\$

Months from the earliest claimed priority date (37 CFR 1.492(f)).

+

TOTAL NATIONAL FEE =

\$ 430.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be

accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property

+

\$

TOTAL FEE ENCLOSED =

\$ 430.00

Amount to be:
refunded

\$

Charged

\$

- a. ☒ A check in the amount of \$430.00 to cover the above fees is enclosed.
- b. ☐ Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees.
A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 08-3284. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not yet been met, a petition to revive (37 CFR 1.127(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Steven J. Hultquist
Intellectual Property/Technology Law
P. O. Box 14329
Research Triangle Park, NC 27709


MARIANNE FUIERER
Registration No. 39,983



526 Rec'd PCT/PTO 1-2 JUL 2001



23448

PATENT TRADEMARK OFFICE

3IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:

Applicants: Sedlacek, et al.

Docket No.: 4121-125

Application No.: 09/857,902

Date Filed: June 8, 2001

Title: SPERMATOGENESIS
PROTEINEXPRESS MAIL CERTIFICATE

I hereby certify that I am mailing the attached documents to the Commissioner for Patents on the date specified, in an envelope addressed to the Commissioner for Patents, Washington, D.C., 20231 and Express Mailed under the provisions of 37 CFR 1.10.

Lee Ann Brown

July 13, 2001

Date

EL831358157US

Express Mail Label Number

EL831358157US

PRELIMINARY AMENDMENT IN U.S. PATENT APPLICATION NO. 09/857,902

Commissioner for Patents
Washington, DC 20231

07/20/2001 HANGUYEN 000000021 09857902

Sir:
01 FC:966

36.00 DP

Prior to examination of the above-identified patent application, please amend the application, as follows:

In the Specification

On page 2, please amend the first, second, third and fourth paragraphs to read as follows:

The present invention is based on applicant's findings that the gene XAP-5 localized in X-chromosomal manner has a partner gene which is localized in autosomal fashion and is expressed in many tissues. For example, the expression can be found in the testicles, it being here especially strong in spermatogenesis, in particular in the stages of primary and secondary spermatocytes as well as the round spermatocytes. The partner gene is referred to as X5L and is localized in the human genome on chromosome 6 in the region 6pter. Applicant isolated and characterized X5L on the PAC clone LLNLp 704K12294Q13. The DNA comprises a coding sequence and an intron and results in an about 1.6 kb long cDNA. It codes for an approximately 37 kD long spermatogenesis protein comprising 325 amino acids and referred to as X5L protein (cf. figures 1, 2 (SEQ ID NO: 1, 2, and 3) and 5, 6). Applicant also found out that mutations in the X5L protein may impair spermatogenesis.

According to the invention applicant's findings are utilized to provide a spermatogenesis protein (X5L protein) comprising the amino acid sequence of figure 1 (SEQ ID NO: 2) or an amino acid sequence differing therefrom by one or several amino acids, a homology of at least 70 % being present between the latter amino acid sequence and the amino acid sequence of figure 1 (SEQ ID NO: 2).

The expression "an amino acid sequence differing by one or several amino acids comprises any amino acid sequence coding for an X5L protein and having a homology of at least 80 % with respect to that of figure 1 (SEQ ID NO: 2). The amino acid sequence may differ from that of figure 1 (SEQ ID NO: 2) by additions, deletions, substitutions and/or inversions of individual amino acids. In

particular, the amino acid sequence may be that of figure 3 (SEQ ID NO: 5)..

Another subject matter of the present invention is a nucleic acid which codes for an X5L protein. The nucleic acid may be an RNA or a DNA, e.g. a cDNA. A DNA is preferred which comprises the following:

(a) The DNA of figure 1 (SEQ ID NO: 1) or a DNA differing therefrom by one or more base pairs, the latter DNA hybridizing with the DNA of figure 1 (SEQ ID NO: 1) and coding for an X5L protein whose amino acid sequence has a homology of at least 80 % to that of figure 1 (SEQ ID NO: 2), or

(b) a DNA related to the DNA of (a) via the degenerated genetic code.

On page 3, please amend the second paragraph to read as follows:

The expression "a DNA differing by one or more base pairs" comprises any DNA sequence coding for an X5L protein, which hybridizes with the DNA of figure 1 (SEQ ID NO: 1) and codes for an X5L protein whose amino acid sequence has a homology of at least 80 % to that of figure 1 (SEQ ID NO: 2). The DNA sequence may differ from the DNA of figure 1 by additions, deletions, substitutions and/or inversions of individual base pairs. In particular, the DNA sequence may be that of figures 2 to 4 (SEQ ID NO: 3, 4, 5 and 6). The expression "hybridization" refers to hybridization under common conditions, in particular at 20°C below the melting point of the DNA sequence.

On page 7, please amend the first, second, third and fourth paragraphs to read as follows:

Figure 1 shows the DNA (SEQ ID NO: 1) and amino acid sequences of a spermatogenesis protein (SEQ ID NO: 2) according to

the invention which comprises 325 amino acids (X5L protein). The DNA sequence is a human cDNA.

Figure 2 shows the sequences of a genomic DNA coding for an X5L protein (SEQ ID NO: 3). The DNA originates from the human genome. The cDNA of figure 1 starts at the -739 base pair. An intron is present between base pairs 828 and 1129. A polyadenylation site is found at the 2658 base pair.

Figure 3 shows the DNA (SEQ ID NO: 4) and amino acid sequences of an X5L protein (SEQ ID NO: 5) comprising 334 amino acids. The DNA sequence is a mouse cDNA.

Figure 4 shows the sequence of a genomic DNA coding for an X5L protein. The DNA originates from the mouse genome. The cDNA of figure 3 starts at the 445 base pair of figure 4 (A) (SEQ ID NO: 6). An intron is present between the base pairs 492-1232 of figure 4 (A). An intron is present between base pairs 1-1136 of figure 4(B) (SEQ ID NO: 7). A polyadenylation sequence is found at the 2306 base pair of figure 4(B).

In the Claims

Please amend claims 1-11 to read as follows:

1. A spermatogenesis protein, comprising the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence differing therefrom by one or more amino acids, wherein a homology of at least 80% exists between the latter amino acid sequence and that of SEQ ID NO: 2.
2. The spermatogenesis protein according to claim 1, comprising the amino acid sequence of SEQ ID NO: 5.

3. A DNA coding for the spermatogenesis protein, comprising:
 - (a) the DNA of SEQ ID NO: 1 or a DNA differing therefrom by one or more base pairs, the latter DNA hybridizing with the DNA of SEQ ID NO: 1 and coding for a spermatogenesis protein whose amino acid sequence has a homology of at least 80% to that of SEQ ID NO: 2, or
 - (b) a DNA related to the DNA from (a) via the degenerated genetic code.
4. The DNA according to claim 3, wherein the latter DNA is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 7.
5. An expression plasmid, comprising the DNA according to claim 3.
6. A transformat, containing the expression plasmid according to claim 5.
7. A method of producing a spermatogenesis protein, comprising the culturing of the transformat according to claim 6 under suitable conditions.
8. Antibodies directed against the spermatogenesis protein according to claim 1.
9. Use of the spermatogenesis protein according to claim 1 for studying or influencing spermatogenesis.
10. Use according to claim 9, wherein the influence of spermatogenesis comprises its activation or inhibition.
11. Use according to claim 9, wherein studying or influencing spermatogenesis comprises a diagnosis and/or treatment of disorders of spermatogenesis.

Please add the following new claims 12-24.

12. An expression plasmid, comprising the DNA according to claim 4.
13. A transformat, containing the expression plasmid according to claim 13.
14. A method of producing a spermatogenesis protein, comprising the culturing of the transformat according to claim 13 under suitable conditions.
15. Antibodies directed against the spermatogenesis protein according to claim 2.
16. Use of the spermatogenesis protein according to claim 2.
17. Use of the spermatogenesis DNA according to claim 3.
18. Use of the spermatogenesis DNA according to claim 4.
19. Use according to claim 16, wherein the influence of spermatogenesis comprises its activation or inhibition.
20. Use according to claim 17, wherein the influence of spermatogenesis comprises its activation or inhibition.
21. Use according to claim 18, wherein the influence of spermatogenesis comprises its activation or inhibition.
22. Use according to claim 16, wherein studying or influencing spermatogenesis comprises a diagnosis and/or treatment of disorders of spermatogenesis.
23. Use according to claim 17, wherein studying or influencing spermatogenesis comprises a diagnosis and/or treatment of disorders of spermatogenesis.

24. Use according to claim 18, wherein studying or influencing spermatogenesis comprises a diagnosis and/or treatment of disorders of spermatogenesis.

REMARKS

A marked-up version of amended paragraphs in the specification and amended claims are included herewith in Appendix A.

Fees Payable

Four new dependent claims are added beyond the number for which a fee has previously been paid, resulting in an added claims fee of \$36.00.

A check in the amount of \$36.00 is submitted herewith in payment of the added claims fee. The U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this amendment, and to credit any excess payment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

It is requested that the examination and prosecution of this application proceed on the basis of claims 1-24 setforth hereinabove.

Respectfully submitted,



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Registration No. 39,983
Attorney for Applicants

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TECHNOLOGY LAW
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Attorney File: 4121-125

APPENDIX A

In the Specification

On page 2, please amend the first, second, third and fourth paragraphs to read as follows:

The present invention is based on applicant's findings that the gene XAP-5 localized in X-chromosomal manner has a partner gene which is localized in autosomal fashion and is expressed in many tissues. For example, the expression can be found in the testicles, it being here especially strong in spermatogenesis, in particular in the stages of primary and secondary spermatocytes as well as the round spermatocytes. The partner gene is referred to as X5L and is localized in the human genome on chromosome 6 in the region 6pter. Applicant isolated and characterized X5L on the PAC clone LLNlp 704K12294Q13. The DNA comprises a coding sequence and an intron and results in an about 1.6 kb long cDNA. It codes for an approximately 37 kD long spermatogenesis protein comprising 325 amino acids and referred to as X5L protein (cf. figures 1, 2 (SEQ ID NO: 1; 2, and 3) and 5, 6). Applicant also found out that mutations in the X5L protein may impair spermatogenesis.

According to the invention applicant's findings are utilized to provide a spermatogenesis protein (X5L protein) comprising the amino acid sequence of figure 1 (SEQ ID NO: 2) or an amino acid sequence differing therefrom by one or several amino acids, a homology of at least 70 % being present between the latter amino acid sequence and the amino acid sequence of figure 1 (SEQ ID NO: 2).

The expression "an amino acid sequence differing by one or several amino acids comprises any amino acid sequence coding for an X5L protein and having a homology of at least 80 % with respect to that of figure 1 (SEQ ID NO: 2). The amino acid sequence may differ from that of figure 1 (SEQ ID NO: 2) by additions, deletions,

substitutions and/or inversions of individual amino acids. In particular, the amino acid sequence may be that of figure 3 (SEQ ID NO: 5).

Another subject matter of the present invention is a nucleic acid which codes for an X5L protein. The nucleic acid may be an RNA or a DNA, e.g. a cDNA. A DNA is preferred which comprises the following:

(a) The DNA of figure 1 (SEQ ID NO: 1) or a DNA differing therefrom by one or more base pairs, the latter DNA hybridizing with the DNA of figure 1 (SEQ ID NO: 1) and coding for an X5L protein whose amino acid sequence has a homology of at least 80 % to that of figure 1 (SEQ ID NO: 2), or

(b) a DNA related to the DNA of (a) via the degenerated genetic code.

On page 3, please amend the second paragraph to read as follows:

The expression "a DNA differing by one or more base pairs" comprises any DNA sequence coding for an X5L protein, which hybridizes with the DNA of figure 1 (SEQ ID NO: 1) and codes for an X5L protein whose amino acid sequence has a homology of at least 80 % to that of figure 1 (SEQ ID NO: 2). The DNA sequence may differ from the DNA of figure 1 by additions, deletions, substitutions and/or inversions of individual base pairs. In particular, the DNA sequence may be that of figures 2 to 4 (SEQ ID NO: 3, 4, 5 and 6). The expression "hybridization" refers to hybridization under common conditions, in particular at 20°C below the melting point of the DNA sequence.

On page 7, please amend the first, second, third and fourth paragraphs to read as follows:

Figure 1 shows the DNA (SEQ ID NO: 1) and amino acid sequences of a spermatogenesis protein (SEQ ID NO: 2) according to

the invention which comprises 325 amino acids (X5L protein). The DNA sequence is a human cDNA.

Figure 2 shows the sequences of a genomic DNA coding for an X5L protein (SEQ ID NO: 3). The DNA originates from the human genome. The cDNA of figure 1 starts at the -739 base pair. An intron is present between base pairs 828 and 1129. A polyadenylation site is found at the 2658 base pair.

Figure 3 shows the DNA (SEQ ID NO: 4) and amino acid sequences of an X5L protein (SEQ ID NO: 5) comprising 334 amino acids. The DNA sequence is a mouse cDNA.

Figure 4 shows the sequence of a genomic DNA coding for an X5L protein. The DNA originates from the mouse genome. The cDNA of figure 3 starts at the 445 base pair of figure 4 (A) (SEQ ID NO: 6). An intron is present between the base pairs 492-1232 of figure 4 (A). An intron is present between base pairs 1-1136 of figure 4 (B) (SEQ ID NO: 7). A polyadenylation sequence is found at the 2306 base pair of figure 4 (B).

In the Claims

Please amend claims 1-11 to read as follows:

1. A spermatogenesis protein, comprising the amino acid sequence of [fig. 1] SEQ ID NO: 2 or an amino acid sequence differing therefrom by one or more amino acids, wherein a homology of at least 80% exists between the latter amino acid sequence and that of [fig. 1] SEQ ID NO: 2.
2. The spermatogenesis protein according to claim 1, comprising the amino acid sequence of [fig. 3] SEQ ID NO: 5.

3. A DNA coding for the spermatogenesis protein [according to claim 1], comprising:
 - (a) the DNA of [fig. 1] SEQ ID NO: 1 or a DNA differing therefrom by one or more base pairs, the latter DNA hybridizing with the DNA of [fig. 1] SEQ ID NO: 1 and coding for a spermatogenesis protein whose amino acid sequence has a homology of at least 80% to that of [fig. 1] SEQ ID NO: 2, or
 - (b) a DNA related to the DNA from (a) via the degenerated genetic code.
4. The DNA according to claim 3, wherein the latter DNA is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 7 [that of fig. 2, fig. 3, or fig. 4].
5. An expression plasmid, comprising the DNA according to claim 3 [or 4].
8. Antibodies directed against the spermatogenesis protein according to claim 1 [or 2].
9. Use of the spermatogenesis protein according to claim 1 [or 2 or a DNA according to claim 3 or 4] for studying or influencing spermatogenesis.

JC03 Rec'd PCT/PTO 08 JUN 2001

SEQUENCE PROTOCOL

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09/857902

JC03 Rec'd PCT/PTC 08 JUN 2001

Spermatogenesis Protein

The present invention relates to a spermatogenesis protein, a DNA coding for such a protein and a method of producing such a protein. The invention also relates to antibodies directed against the protein and to the use of the DNA and the protein for studying or influencing spermatogenesis.

Spermatogenesis is referred to as the formation of sperms in mammals or humans. This formation takes place in the testicles. During spermatogenesis, in particular the pachytene stage of meiosis, the X and Y chromosomes accumulate and form what is called a sex body. The X and Y chromosomes are present inactively therein, i.e. they are not transcribed.

It has now turned out that some of the genes of the X and Y chromosomes have partner genes which are localized in autosomal manner. They are expressed *inter alia* in the testicles, so that their gene products have compensatory functions in spermatogenesis as regards the corresponding inactivated genes of the X and Y chromosomes.

Influencing spermatogenesis is still a major problem. This is in particular due to the fact that spermatogenesis is not understood in detail.

It is thus the object of the present invention to provide a product by which spermatogenesis can be studied and possibilities can optionally be shown by means of which spermatogenesis can be influenced.

According to the invention this is achieved by the subject matters defined in the claims.

The present invention is based on applicant's findings that the gene XAP-5 localized in X-chromosomal manner has a partner gene which is localized in autosomal fashion and is expressed in many tissues. For example, the expression can be found in the testicles, it being here especially strong in spermatogenesis, in particular in the stages of primary and secondary spermatocytes as well as the round spermatocytes. The partner gene is referred to as X5L and is localized in the human genome on chromosome 6 in the region 6pter. Applicant isolated and characterized X5L on the PAC clone LLNLP 704K12294Q13. The DNA comprises a coding sequence and an intron and results in an about 1.6 kb long cDNA. It codes for an approximately 37 kD long spermatogenesis protein comprising 325 amino acids and referred to as X5L protein (cf. figures 1, 2 and 5, 6). Applicant also found out that mutations in the X5L protein may impair spermatogenesis.

According to the invention applicant's findings are utilized to provide a spermatogenesis protein (X5L protein) comprising the amino acid sequence of figure 1 or an amino acid sequence differing therefrom by one or several amino acids, a homology of at least 70 % being present between the latter amino acid sequence and the amino acid sequence of figure 1.

The expression "an amino acid sequence differing by one or several amino acids comprises any amino acid sequence coding for an X5L protein and having a homology of at least 80 % with respect to that of figure 1. The amino acid sequence may differ from that of figure 1 by additions, deletions, substitutions and/or inversions of individual amino acids. In particular, the amino acid sequence may be that of figure 3.

Another subject matter of the present invention is a nucleic acid which codes for an X5L protein. The nucleic acid may be an RNA or a DNA, e.g. a cDNA. A DNA is preferred which comprises the following:

- (a) The DNA of figure 1 or a DNA differing therefrom by one or more base pairs, the latter DNA hybridizing with the

DNA of figure 1 and coding for an X5L protein whose amino acid sequence has a homology of at least 80 % to that of figure 1, or

- (b) a DNA related to the DNA of (a) via the degenerated genetic code.

The expression "a DNA differing by one or more base pairs" comprises any DNA sequence coding for an X5L protein, which hybridizes with the DNA of figure 1 and codes for an X5L protein whose amino acid sequence has a homology of at least 80 % to that of figure 1. The DNA sequence may differ from the DNA of figure 1 by additions, deletions, substitutions and/or inversions of individual base pairs. In particular, the DNA sequence may be that of figures 2 to 4. The expression "hybridization" refers to hybridization under common conditions, in particular at 20°C below the melting point of the DNA sequence.

The DNAs of figures 1 to 4 were deposited as h-X5L-c, h-X5L-g, m-X5L-c and m-X5L-g on November 26, 1998 with DSMZ (*Deutsche Sammlung von Mikroorganismen und Zellkulturen* [Germany-type collection of microorganisms and cell cultures]) under DSM 12550, DSM 123553, DSM 12552 and DSM 12551, respectively.

A DNA according to the invention may be present as such or in combination with any other DNA. In particular, a DNA according to the invention which codes for an X5L protein may be present in an expression vector. A person skilled in the art is familiar with examples thereof. In the case of an expression vector for *E. coli* these are e.g. pGEMEX, pUC derivatives, pGEX-2T, pET3b, and pQE-8. For the expression in yeast e.g. pY100 and Ycpad1 have to be mentioned, while e.g. pKCR, pEFBOS, cDM8 and pCEV4 have to be indicated for the expression in animal cells. The baculovirus expression vector pAcSGHisNT-A is particularly suitable for the expression in insect cells.

The person skilled in the art knows suitable cells to express the DNA according to the invention which is present in an expression vector. Examples of such cells comprise the *E. coli* strains HB101, DH1, x1776, JM101, JM 109, BL 21 and SG 13009, the yeast strain *Saccharomyces cerevisiae* and the animal cells L, NIH 3T3, FM3A, CHO, COS, Vero and HeLa as well as the insect cells sf9.

The person skilled in the art knows how to insert the DNA according to the invention in an expression vector. He is also familiar with the fact that this DNA can be inserted in combination with a DNA coding for another protein or peptide, so that the DNA according to the invention can be expressed in the form of a fusion protein.

Moreover, the person skilled in the art knows conditions of culturing transformed or transfected cells. He also knows methods of isolating and purifying the protein or fusion protein expressed by the DNA according to the invention.

Another subject matter of the present invention is an antibody directed against an above protein or fusion protein. Such an antibody may be made by common methods. It may be polyclonal or monoclonal. For its production it is favorable to immunize animals - in particular rabbits or chickens for a polyclonal antibody and mice for a monoclonal antibody - with an above (fusion) protein or with fragments thereof. Further boosters of the animals may be made with the same (fusion) protein or with fragments thereof. The polyclonal antibody may then be obtained from the serum or egg yolk of the animals. For obtaining the monoclonal antibody animal spleen cells are fused with myeloma cells.

Another subject matter of the present invention is a kit. Such a kit comprises one or more of the following components:

- (a) a DNA according to the invention,
- (b) a spermatogenesis protein according to the invention (X5L protein),

- (c) an antibody according to the invention, and
- (d) common auxiliary agents, such as carriers, buffers, solvents, controls, etc.

One or more representatives of the individual components may be present each. As to the individual terms reference is made to the above statements. They apply here correspondingly.

The present invention enables the study of spermatogenesis. An X5L protein may be detected by means of an antibody according to the invention. A relationship may be established between an X5L protein and processes occurring in spermatogenesis. Furthermore, an autoantibody directed against this protein may be detected with an X5L protein. Both detections may be made by common methods, in particular a Western blot, an ELISA, an immunoprecipitation or by immunofluorescence. In addition, the organization and expression of the gene coding for an X5L protein may be detected with a nucleic acid according to the invention. This detection may be made as usual, in particular in a Southern blot, by *in situ* hybridization or by PCR.

Besides, the present invention is also suitable to take steps for inhibiting, or increasing the activity of, an X5L protein in persons. An X5L protein may be inhibited by means of an antibody according to the invention. On the other hand, the amount of an X5L protein in persons can be increased using an X5L protein, in particular after linkage to a protein which is not considered foreign by the body, e.g. transferrin or BSA. The same can also be achieved correspondingly with a nucleic acid according to the invention, in particular a DNA which is controlled by a constitutive promoter or a promoter inducible in certain tissues and after its expression results in the provision of an X5L proteins in the person or in certain tissues, e.g. testicles.

Thus, the present invention relates to means for studying spermatogenesis and influencing it by regulating it. The latter comprises both its activation and its inhibition. In

particular, the present invention provides means serving for diagnosing and treating disorders of spermatogenesis.

Brief Description of the Drawings.

Figure 1 shows the DNA and amino acid sequences of a spermatogenesis protein according to the invention which comprises 325 amino acids (X5L protein). The DNA sequence is a human cDNA.

Figure 2 shows the sequences of a genomic DNA coding for an X5L protein. The DNA originates from the human genome. The cDNA of figure 1 starts at the -739 base pair. An intron is present between base pairs 828 and 1129. A polyadenylation site is found at the 2658 base pair.

Figure 3 shows the DNA and amino acid sequences of an X5L protein comprising 334 amino acids. The DNA sequence is a mouse cDNA.

Figure 4 shows the sequence of a genomic DNA coding for an X5L protein. The DNA originates from the mouse genome. The cDNA of figure 3 starts at the 445 base pair of figure 4(A). An intron is present between the base pairs 492-1232 of figure 4(A). An intron is present between base pairs 1-1136 of figure 4(B). A polyadenylation sequence is found at the 2306 base pair of figure 4(B).

Figure 5 shows the detection of mRNA of an X5L protein in tissues.

Figure 6 shows the detection of mRNA of an X5L protein in testicles. The presence of such an mRNA is limited to tubuli (figure 6(A)). At a cellular level, mRNA of an X5L protein is present in the stages of primary and secondary spermatocytes (stars) and the round spermatocytes (RS). Mature sperms are characterized by (MS) and spermatogoniums are marked by (arrowheads). Sertoli cells (arrows) and Leydig cells (L) have no mRNA of an X5L protein.

The present invention is explained by the below examples.

Example 1: Detection of mRNA of an X5L protein in tissues

(A)

RNA blots of human tissues such as pancreas, suprarenal medulla, thyroid gland, adrenal cortex, testicles, thymus, small intestine, stomach, fetal brain, fetal lungs, fetal liver, and fetal kidney, obtained from Clontech, are subjected to hybridization. A [α^{32} P]dCTP-labeled X5L protein-specific DNA which lies between base pairs 1073 and 1409 of the DNA of figure 1 is used as hybridization sample. The hybridization is carried out overnight followed by wash steps under common conditions. The blots are also hybridized with a radioactive β -actin sample for the purpose of control (cf. figure 5).

It turns out that mRNA of an X5L protein is expressed in the most varying tissues. The size of the expressed mRNA is 1.7 or 4.3 kb, which is due to differing polyadenylation signals of the DNA of figure 1. It also shows that the expression of mRNA of an X5L protein is the strongest in testicles.

(B)

An RNA *in situ* hybridization is carried out with mouse-testicle tissue. For this purpose, reference is made to the method by Wilkinson, D.G. (1992), Oxford University Press, New York. Antisense or sense RNA samples are used which correspond to base pairs 5-1169 of the DNA of figure 1.

It shows that a strong expression of mRNA of an X5L protein takes place in testicle tissue. It also turns out that the expression is limited to tubuli. At a cellular level, an expression of mRNA of an X5L protein shows in the stages of the primary and secondary spermatocytes as well as the round spermatocytes. Spermatogoniums, mature Sertoli cells and Leydig cells, however, show no expression of mRNA of an X5L protein.

**Example 2: Production and purification of a
 spermatogenesis protein according to the
 invention (X5L protein)**

The DNA of figure 1 is provided with BAMHI linkers subsequently cleaved using BamHI and inserted in the BamHI-cleaved expression vector pQE-8 (Quiagen company). The expression plasmid pQE-8/X5L is obtained. Such a plasmid codes for a fusion protein of 6 histidine residues (N terminus partner) and the X5L protein of figure 1 according to the invention (C terminus partner). pQE-8/X5L is used for transforming *E. coli* SG 13009 (cf. Gottesman, S. et al., J. Bacteriol. 148, (1981), 265-273). The bacteria are cultured in an LB broth with 100 µg/ml ampicillin and 25 µg/ml kanamycin and induced for 4 h using 60 µM isopropyl-β-D-thiogalactopyranoside (IPTG). Lysis of the bacteria is achieved by adding 6 M guanidine hydrochloride, and a chromatography (Ni-NTA resin) is subsequently carried out with the lysate in the presence of 8 M urea in accordance with the instructions from the manufacturer (Qiagen) of the chromatography material. The bound fusion protein is eluted in a buffer with pH 3.5. After its neutralization, the fusion protein is subjected to 18 % SDS polyacrylamide gel electrophoresis and stained using coomassie blue (cf. Thomas, J.O. and Kornberg, R.D., J. Mol. Biol. 149 (1975), 709-733).

It shows that a (fusion) protein according to the invention can be prepared in highly pure form.

**Example 3: Production and detection of an antibody
 according to the invention**

A fusion protein of Example 2 according to the invention is subjected to 18 % SDS polyacrylamide gel electrophoresis. After staining of the gel using 4 M sodium acetate an about 37 kD band is excised from the gel and incubated in phosphate-buffered common salt solution. Gel pieces are sedimented before the protein concentration of the

supernatant is determined by SDS polyacrylamide gel electrophoresis which is followed by coomassie blue staining. Animals are immunized as follows using the gel-purified fusion protein.

Immunization protocol for polyclonal antibodies in rabbits

35 μ g of gel-purified fusion protein in 0.7 ml PBS and 0.7 ml of complete or incomplete Freund's adjuvant are used per immunization:

- Day 0: 1st immunization (complete Freund's adjuvant)
- Day 14: 2nd immunization (incomplete Freund's adjuvant; icFA)
- Day 28: 3rd immunization (icFA)
- Day 56: 4th immunization (icFA)
- Day 80: bleeding to death.

The rabbit serum is tested in an immunoblot. For this purpose, a fusion protein of Example 1 according to the invention is subjected to SDS polyacrylamide gel electrophoresis and transferred to a nitrocellulose filter (cf. Khyse-Andersen, J., J. Biochem. Biophys. Meth. 10 (1984), 203-209). The Western blot analysis was carried out as described in Bock, C.-T. et al., Virus Genes 8, (1994), 215-229. For this purpose, the nitrocellulose filter is incubated with a first antibody at 37°C for one hour. This antibody is the rabbit serum (1:10000 in PBS). After several wash steps using PBS, the nitrocellulose filter is incubated with a second antibody. This antibody is an alkaline phosphatase-coupled monoclonal goat anti-rabbit IgG antibody (Dianova company) (1:5000) in PBS. 30 minutes of incubation at 37°C are followed by several wash steps using PBS and subsequently by the alkaline phosphatase detection reaction with developer solution (36 μ M 5'-bromo-4-chloro-3-indolylphosphate, 400 μ M nitro blue tetrazolium, 100 mM Tris-HCl, pH 9.5, 100 mM NaCl, 5 mM MgCl₂) at room temperature until bands become visible.

It shows that polyclonal antibodies according to the

invention can be prepared.

Immunization protocol for polyclonal antibodies in chickens

40 μ g of gel-purified fusion protein in 0.8 ml PBS and 0.8 ml of complete or incomplete Freund's adjuvant are used per immunization.

Day 0: 1st immunization (complete Freund's adjuvant)
Day 28: 2nd immunization (incomplete Freund's adjuvant; icFA)
Day 50: 3rd immunization (icFA)

Antibodies are extracted from egg yolk and tested in a Western blot. Polyclonal antibodies according to the invention are detected.

Immunization protocol for monoclonal antibodies in mice

12 μ g of gel-purified fusion protein in 0.25 ml PBS and 0.25 ml of complete or incomplete Freund's adjuvant are used per immunization. The fusion protein is dissolved in 0.5 ml (without adjuvant) in the 4th immunization.

Day 0: 1st immunization (complete Freund's adjuvant)
Day 28: 2nd immunization (incomplete Freund's adjuvant; icFA)
Day 56: 3rd immunization (icFA)
Day 84: 4th immunization (PBS)
Day 87: fusion.

Supernatants of hybridomas are tested in a Western blot. Monoclonal antibodies according to the invention are identified.

Claims

1. A spermatogenesis protein, comprising the amino acid sequence of fig. 1 or an amino acid sequence differing therefrom by one or more amino acids, wherein a homology of at least 80 % exists between the latter amino acid sequence and that of fig. 1.
2. The spermatogenesis protein according to claim 1, comprising the amino acid sequence of fig. 3.
3. A DNA coding for the spermatogenesis protein according to claim 1, comprising:
 - (a) the DNA of fig. 1 or a DNA differing therefrom by one or more base pairs, the latter DNA hybridizing with the DNA of fig. 1 and coding for a spermatogenesis protein whose amino acid sequence has a homology of at least 80 % to that of fig. 1, or
 - (b) a DNA related to the DNA from (a) via the degenerated genetic code.
4. The DNA according to claim 3, wherein the DNA is that of fig. 2, fig. 3 or fig. 4.
5. An expression plasmid, comprising the DNA according to claim 3 or 4.
6. A transformant, containing the expression plasmid according to claim 5.
7. A method of producing a spermatogenesis protein, comprising the culturing of the transformant according to claim 6 under suitable conditions.
8. Antibodies directed against the spermatogenesis protein according to claim 1 or 2.

9. Use of the spermatogenesis protein according to claim 1 or 2 or a DNA according to claim 3 or 4 for studying or influencing spermatogenesis.

10. Use according to claim 9, wherein the influence of spermatogenesis comprises its activation or inhibition.

11. Use according to claim 9, wherein studying or influencing spermatogenesis comprises a diagnosis and/or treatment of disorders of spermatogenesis.

Abstract of the Disclosure

The present invention relates to a spermatogenesis protein, a DNA coding for such a protein and a method of producing such a protein. The invention also relates to antibodies directed against the protein and the use of the DNA and the protein for studying or influencing spermatogenesis.

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10 30 50 70 90
 AGAGCCCGGGCCAGTGGGCTCTGCTCTTGGGTGGTCTCTGGAGGTCAGCTCCCGGTGTCTCCGCTCGACAGGGGTGTGGGCAAG
 110 130 150 170
 GCCCATCTGGGTAGGCGCGGGCCATGGCCAGTACAGGGCCCATGGCCAGGAGGCGGTGCTGCACTGCTCTCAAGAGCGCGCAAG
 H A Q Y K G T X R R E A G R A N H L L L X K R E S
 190 210 230 250 270
 GCAGCGGGAGCAGATGAGAGTGGTCTGAGCAGCCGATCCCGAGGAGACCTCTCTCAAGTCCAGGTGACAGAGAGGTGTCTCGCGCATTA
 Q R E Q H E V L K Q R I A E E T I L K S Q V D K R F S A H Y
 290 310 330 350
 CGACCCGCTGGAGCGAGTGAATCCAGCAGCGTGGGCTGGTGACCTCAACGACACTCAAGGCCCGCCAGGAGGCCCTGGTCAGGGA
 D A V E A E L K S S T V G L V T L N D N K A R Q E A L V R E
 370 390 410 430 450
 GCGCGAGCGCCAGTGGCCAGCGCCAGCACCTGAGGAGCAGCGGCTGACGAGCAGCGCGCAGCGGAGCAGGAGCAGCGCGCGAGCG
 R E R Q L A X R Q H L E E Q R L Q Q E A Q R E Q E Q R R E R
 470 490 510 530
 CAAGCTTAAGATCTCTCTGCTGCTTTGCACTAGACGACCTCGATGACGAGCGCAGCTCGCGGAGCGCGCGCGCGCGCGCGCGCG
 K R K I S C L S F A L D D L D D Q A D A A E A R R A G N L G
 550 570 590 610 630
 CAAGACCGCGACCTGGACCCAGCTTCTGCGAGCCGCGACCGCGAGCGAGAGAGACCGCGCTGCGAGGAGCTGCGCGAAGAGT
 R N P D V D T S F L P D R D R E E E E N S A E E L R E G W
 650 670 690 710
 CGAGGCGCAGCGCGAGAAAGTGAAGGACGAGAGATGAGAGTCACTTCACTACTGGGACCGGCTCGGCGACCGCGCGCAGCTCGCGGT
 E A Q R E K V X D S E H E V T F S Y W D G S G H R R T V R V
 730 750 770 790 810
 GCGCAAGGCGCAACGCTGACGACCTCTCTGAAGAGCGGCTGCGAGGCGTGGCGAGGACTCTCTGAGCTGCGCTCGCGCGCGCTGCA
 R K G N T V Q Q F L K K A L Q G L R K D F L Z L R S A G V E
 830 850 870 890
 CGAGCTCATGTTTCATCAAGAGGAGCCTCACTCTGCGCGCACTACCACTCTTACGACTCATCATCGCGAGCGCGAGCGCGCGAGAGCGG
 Q L M P I K E D L I L P H Y N T F Y D F I I A R R A R G R S G
 910 930 950 970 990
 GCGGCTCTCTCAGCTTCGATGTGCAAGATGCTGCGGCTGCTGAGCGAGCGCCACCATGAGAGAGGAGGAGTGGCAGCGCGCGCAAGTGGT
 P L F S F D V H D D V R L L S D A T H E K D E S H A G K R V V
 1010 1030 1050 1070
 GCTCGCGAGCTGGTACGAGAGAAACAGGACATCTCTCCCGCGCAGCGGCTGGGAGGCTATGACCCCGAGAGAGTGGGACAGTACAC
 L R S W Y E K N K H I F P A S R W E A Y D P E K K W D K Y T
 1090 1110 1130 1150 1170
 CATCGGCTACACCGCGCTGCCAGAGCGGAAACCGCGGCTGGGGGAGCACTCATTTCTAGCGCCCATCACAGTCACTGATTTCGTG
 I R
 1190 1210 1230 1250
 ACCTTGATTCTCTCCCCAAATTAAATAAGACAGAGGGTCTCATGATTCACATTGGTGTGTGCTATGCTGATGTTATGCTTTGGTGGC
 1270 1290 1310 1330 1350
 TTGCTTGGTCTTTTCTGAGTATTTTGAAGTGTGCCACCTGGATTGGTGCATGCTGCTGCTGAGCTGTATTGAACCATGACTGGGCCCCAC
 1370 1390 1410 1430
 TGTGACAGGAAATAGAAATAGGAGGACATTTTCTACCTGGTGTTATGAGCATGGACTGGGGGCCACGACTGACTGAGTTTGATTCCG
 1450 1470 1490 1510 1530
 GACACAGGCTCTCTCTGCTGTGTAGTTTTCGGTAAGCTTATTAAACCCCATGCGCTAGTTTGGTCACCTGATAAAGGAAATCAACAAG
 1550 1570 1590 1610
 GCACCTACTTTAAGAGTGTGTGAGTATTAAGTGAATTAACTTTGTAAACCGCTTAGCTCTTAATAAATGTTCTGTGTATTATA

Fig. 1

10	30	50	70	90
GAACGGTCACGAAACATGAACCTGGTCTGCCCTGCTCTTGAGAGATTACATGTGGAACATGGCATGTGTAGAGGCTCACAGTAAGAACAATG	110	130	150	170
CTACACTTTAACTCAGTGTCCCAATGGTTATTAGAGCTTAGAACCCGGGGGAAATGCTGTATAGAGAGAGGTCAAAACAGCTCAGTGCAGG	190	210	230	250
TTTGTTCAGGAACTGGGGGCGAGTAGGGTTCTATTATCAAGAAATGGTTGTGTGGGGCCATAAGAAAGATTACAGGCGAGTGGTGGG	270	290	310	330
CAGGTAAATTCTTCAGAGACGCGACAGCGGGTAGCATCAGAGGGGGGAGGAGGCGTTTGAGAGACAGGCGCGTGTTCGACAGGCTCTCTG	350	370	390	410
GGTGGCCACAGCAGCTTGGCGTGCACCAATTTGCTTCTGCGTGTACAGCTGGGCAAGAAAGGCTCAGCACGCACGACAGCAGGTG	430	450	470	490
GGGGCCCGGCTCTGCCCACTAGCTGAAACAGAGAGCGCCCGGCGACGCCACGGCTGGGCAAGGCGGCGTCTCTCGAGATCTCTCCGG	510	530	550	570
CGCTGGCCCGGCGCCACAGAGAGCACTGCGCTTACAGGAGCGCGCGAGCTTCTCCAGGGCGCGCTCCCCCGCAGGGGGCGATTCACCTCC	590	610	630	650
ACTTCTCTGTTCGCGAGCGCGCTTACAGAGGCTGGCACTCTCTTCAAGGCGCGCTCTCCGCGAGGCGCGGACCGCGCTCCACTTCTCT	670	690	710	730
GTGTCCACGGCTGTGCGCAAGCGCGGGCGAGTGGCGCTCTCTCTGTGGTGTCTCTGTGGAGTCAGCTCTCCGCGTGTCTCCGCTG	750	770	790	810
ACAGGTGCTTGGGCAATAGGCTGGCTCTAGCTAGCGCAACCTCTCTGTATGCAGCTCCCAAATCTCAGCGCTGGCTCAGGCAATGGC	830	850	870	890
AGCCACCGCTTACGTGGGCGCTTCCGATTTGCATTATATGAGTCAAAAGAAATGTGAATTTGGTCTCTGGTGACACTGTCAAGTTG	910	930	950	970
GTGGTTACCTAGCAGTGTGGCCAGCGCCCTGAGAGCTTCATCACTCGCGGAAAGCCCTGTGTAGGAGGCGCGAGAGTGCAGATCTCCCGC	990	1010	1030	1050
CGTTCGCTGGCGCCCTCTTACTCGCGGCTTTCTCTCTTTCTGCTGAAAGCGCCATCGGTTAGCGCGCGCGCTTACGCGCATACAGGGC	1070	1090	1110	1130
ACCATTCGCGCGGAGCGAGCGCTGCCATGCATCTCTCAAGAGAGCGCGAGCGAGCGGAGCAGATGAGGTTCTGAAGCAGCGCATCTGCCT	1150	1170	1190	1210
GAGGAGACCATCTCTCAAGTGTGAGTGGAGAGAGGTTCTTGGCGCATTTACGAGCGCTGTGAGCGCCCGCTGAAGTCCAGACAGCGTGGG	1230	1250	1270	1290
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	1310	1330	1350	1370
CAGCGGCTGACAGGAGCGCGAGCGGAGCAGAGCAGCGCGCGAGCGCGCAGCGTAAAGATCTCTGCTGCTGTCTTTGCACTAGACGAG	1390	1410	1430	1450
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	1470	1490	1510	1530
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	1550	1570	1590	1610
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	1630	1650	1670	1690
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	1710	1730	1750	1770
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	1790	1810	1830	1850
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	1870	1890	1910	1930
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	1950	1970	1990	2010
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2030	2050	2070	2090
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2110	2130	2150	2170
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2190	2210	2230	2250
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2270	2290	2310	2330
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2350	2370	2390	2410
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2430	2450	2470	2490
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2510	2530	2550	2570
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2590	2610	2630	2650
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2670	2690	2710	2730
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2750	2770	2790	2810
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2830	2850	2870	2890
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2910	2930	2950	2970
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	2990	3010	3030	3050
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	3070	3090	3110	3130
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	3150	3170	3190	3210
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	3230	3250	3270	3290
CTGTGACCTTGAACGATGAAGGCGCGGCGAGAGCGGCTGTGAGGAGCGCGCGAGCTGGCCATAGCGCGCAGGCACTTGAGAGG	3310	3330</		

Fig. 2 (cont'd)

2350 2370 2390 2410 2430
ATTGCTGCATGCTCTGCTGAGCTGTATTGAACCATGACTGGGCCCCACTGTCAGACAGAAAATAGAAATAGGAGGCACATTTTACCT
2450 2470 2490 2510
GGTGGTTATGAGCATGGACTTGGGGGCCACAGTGACTGAGTTTGATTCCCGACACAGCCCTCCTCCTTGCCTGTGTAGTTTGGGTAAGCTT
2530 2550 2570 2590 2610
ATTAAACCCCATGCCCTCAGTTTGGTCACTCTGTAAGGAAATAACAAGAGCACTTACTTTATAAGATTGATGTGAGTATTAAGTGAATT
2630 2650 2670 2690
AATATTTGTAAACGCTTAGCTCTTAATAAATGTTCTGTTGTTATTATGTTTGGTTAATTTATTTAAAGGACTGCAATGACCTA
2710 2730 2750 2770 2790
GTTCAAGAACTATTTGAGGGCAAGGTGGACCTGCCCATCACTGTGTCAGGATCAGCAGTTGCCAGCAGGAGGGGGGCTAGCAAAGGTTGG
2810 2830 2850 2870
GGAGCAGCCCCCTCTAGTGGGCTTAGCTGGGTGTTTAGCCCAAGTTAGGAGGACAGTGAGCTAATGCAAGTAGCCTGCAG

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10 30 50 70 90
 ATTGCGAAAGCACCAGAAAGAGCTCTGGCTCATACTCAAAAGCTGCGAGAATCTGTGAATGACATCAGACCCAGAAAGGCTACCAAG
 110 130 150 170
 AAACAGGGACTGGCGAGGCGAAAAGCCCTTGGCTGAATGCGAGCATGGCGCAGTACAAAGCGACCATGGCGGAAGCTGGCGGGGCCAT
 H A Q Y K G T M R E A C G R A M
 190 210 230 250 270
 GCACCTGATCAGAAAGCTGTGAGAGCAGAGCGAGATGGAGGTGCTGAACGAGCGCATGCGAGGAGACCATCATGAACTCAAAAGT
 H L I K K K R E R Q K E Q M E V L K Q R I A E E T I N K S K V
 290 310 330 350
 GGACAGAAAGTTCTGCGCACTACGACGCCGTGGAGGCCGAGCTGAAGTCCAGTACCGTGGCGCTGGTACCCCTGAATGACATGAAGCG
 D K K K F S A H Y D A V E A E L K S S T V G L V T L N D M K A
 370 390 410 430 450
 CAAGCAGGAGGCGCTGCTGAGGAGCGCGGAGATGCGCTGGCCAAAGAGGAGCAGCTGGAGCAACCGCGGATACAGCTGGAGATGCTGG
 K Q E A L L R E R S M Q L A K R R Q L E Q R R I Q L E M L R
 470 490 510 530
 CGAGAGGAGCGAAGCGAGGCGCAGGCTCAGATCTCCAACTGTCTTTCACCTTGGAGCAGGAAGAAGGTGACCAAGAGGAGCAGCGG
 E K E R R R R E R K K K I S N L S I T L D E E E G D Q E O S R
 550 570 590 610 630
 CCAGCCGAGAGTCCGAGGCCCGCAGCTGTGAGCCAGAGAACTTGGCCAGAAATCCGATGTGACACAGAGCTCTCTGCCCGACCG
 Q A S S A E A E S A G A K K N L G K R N P D V D T S F L P D R
 650 670 690 710
 CGAGCCGAGAGGAGGAGGAGACCGCTTGCCTGAGGAATCTCGGAGCAGCTGGAGGCCAGAGCCGAGAGGCTGAAGCGCGAGGAGCTGGA
 E R E E E E M R L R S E L R Q E W S A K R E K V K G S E V E
 730 750 770 790 810
 GATCACTTTCAGCTACTGGGATGGCTCCGACACCGCGGACGGTGGCGATGAGCAAGGAGCAGCAGGCTGACAGCTTCTGAAGCGCGG
 I T P S Y W D G S G H R R T V R M S K G S T V Q Q F L X R A
 830 850 870 890
 GCTGAGCGGCTGGCGGAGCTTCCGGGAGCTGGCGGAGCGGCGGCTGAGAGCTCACTTACCTCAAGAGGATCTCATCTCTGCGCGC
 L Q G G L R R D F R E L R A A G V E Q L M Y V K E O L I L F H
 910 930 950 970 990
 CTATCACACCTTCTACGACTTCATCTGTGGCCTAAAGCCCGGGCGAGAGCGCGCGGCTCTTCAGCTTCGACCTGCAGCTGCGGCGT
 Y H T F Y D F I V A X A R G K S G F L F S F D V H D D V R L
 1010 1030 1050 1070
 GCTGAGCGATGCGAGTGGAGAAAGATGACTCACACCGCGGCAAGGTGGTGGCTTCGAGCTGGTACGAGAGAACAGACAGCAGCATCTTCC
 L S D A T M E K D E S H A G K V V L R S W Y E X N K H I F P
 1090 1110 1130 1150 1170
 TCCAGCCCGTGGAGCGCTTACGACCCCGAGAAAGTGGACAGGTACACCATCGGTGATGCCAAGTCCAGATTGGGAGCCTTACTC
 A S R W D P Y D P E K K W D R Y T I R
 1190 1210
 CCTAATATCGAAAATTAAATAACAGAGGCTCCCGTAAATCGGA

Fig. 3

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      10              30              50              70              90
CTAAACCTGAAAGTTATTCTGATCAACCATATACCACTGCAAAATGGAGTCAGAGCTTTCTGTCTCTCTGTAGCTAAGATCACT
      110              130              150              170
AATGAGTTATTGTATGAAAGGCAATAAAATCATCGTCTCTGGAGAGTGCCAAATACTTTCAGACTAGTGATATCAGCTAAACTCTTTAGTAA
      190              210              230              250              270
ACAACCTACACACAAAATTTAATCTGTAAATAATCAAAGGCCCAAGTGAACACGACAGTCCAGGAAAACCTTCATGGGAGCATTCGCATT
      290              310              330              350
CAGTTGTCAAGAGATCAGACGCTGGCAGCAGGACTGCATCCATCAGTCACTCCAACTCGGCAGTTATACACGACCAACCACTGATTGGCC
      370              390              410              430              450
CAATCTCTGTCTCGATTGGTTAGAGCCTGCCCCTAGCAGTTGGCCAAATGTTTTCATATTTTCTGTGTCACTTAGAACAAACAATATTGGC
      470              490              510              530
AAAAGCACCCAGAGGAAGATCTTGGCTCAATACATCAAAGGTGAGGGGCTGGCTTGCAATCCAGCTGGGGCAGATGTGGAGGTACAGC
      550              570              590              610              630
TCTTTAACTCGAGTAAACCAATTGTGAAGGAGTTGAATGTAGAGGAAAGGAATTGTGTCCATTATCTCGAAGCAGGGGAGACTAAAT
      650              670              690              710
GAGCCCTATCGGTGACATAAATCAACATTTTTATTGTAATTTAGGAATCACAACAGTGAAGGAGGAGGAAGATGCTCTAAAGGGCTAT
      730              750              770              790              810
GACATATGCTCTAGGAAATAGAAATGGGGCTTCTTCTCTCAATTGTTTGCCTTTCACTGCTGTGTCAAAGCAACCTAAGGAGGAGGA
      830              850              870              890
AAGGGTTTAAATTGATTGATGACTCACAATTAAATCTGTGACAGCAAGTTGGCAGAAGCAGGAGTCAATGTTGTTCTGTAGTCAGAA
      910              930              950              970              990
AAGCCGAGCAAGATAAGGAGCTGCGTTCACTGCGCTTTCCCTATCTCTGCTTTCTACTAGGTTCTGAGACTCACGCCCATGGGCATGTTAAG
      1010              1030              1050              1070
GCCATGTTCAAGATGTTTGTCTTTCCCTCACTTAATCTTTCTGAAATACTCCCAAGACACATGCCCAAGAGCTGTGTATCCTTAAGG
      1090              1110              1130              1150              1170
TTCMAATCTCTGTAGTTGACAAGATTAAACATTAACATGAGTCTCACTCTTAACAGGTCTGATACCTGTTAGCTTATAGTACTGAAA
      1190              1210              1230
GCATACTGAAGGCTTCTGTCTCTGCTAGATTGCTCTGAATCTCTCTTTCTGCGACTGCAG

```

Fig. 4 (A)

10 30 50 70 90
GAATTCAAACAGCCAGGAGACGATGAÖCTTTAAAGCAGCTTGCATATCAAAGAAAGAAAGATGCTACGGAAATGCGCGAGGAAC
110 130 150 170 190
TTTAGACCTTTGGATGACATGGAATGTCTAGAGCAAGCÄCTGTTTGGGAGCTATGCGGCTGAATGGTGTCTCTCAGGGGAAACAAGAGG
210 230 250 270
TTTGGGGACÖCAGTTTGGAGTTTGGAAAGAGTTTGAATAGGAGTGCAGCTGTTCACTGGGATGAGAGCTCACCAGTAAAGAGAGGAC
290 310 330 350
TACAGAAGGTTTGGAGAGCCTAGAGAGGCGGTCAATTCAAGTTGAGTCCAATTAAATTAAGAGATCTCTCTTTCCCTTGACTAGAG
370 390 410 430 450
CACAGAGAAACACTTTGTÄCTTTGGCCCACTCTGTGTCÄTGCAGTTCÖCCTGATGTCTTGTCTCTCACGCGAAGGAGGAGGAGCTCAG
470 490 510 530 550
AGTTCTTTTGTACTTTGACACTGACACAAAGTGAÖTTCACATAAACTCCATGCAGAAATCGTCTCTTAAAGCTTGTGCTAGGATGAAT
570 590 610 630
GCTCCTTGGGACTCTGCAAGACATAACTTAACTGGGAGCTTAACTTAGCÄTCACTCCACTCCAGGTGCAGTAGGGGAGGCTTTCACGG
650 670 690 710 730
ACTCTTTTCTTCTCTGCTTCTGTCTCTGCGAGGATGGGCTCCACAAGGCGCAGGTACTATCTTAAAGGCCAAACCCCTCTCATGGAG
750 770 790 810
ACACGGTTTCTCACTTGACCCAGCTTCACTGTGGCTAGTCTTCAGGAAACCCAGGCCCAAGGCTCTCTCATTTGCTCTGCTTGCATGGCT
830 850 870 890
GTGCATGACGACAGACGGGAGCATGTGGTTTGTCTGTCTGAGCAACCACTCTACATGCAAAACCCCTCAAACCTACTGTACTAAGCTAGT
910 930 950 970 990
GTCCATCTAGGCTTACTCAGTGTGAAGTAAATTTGCTCÖTGTGGTCAAGTATGTGCTTTCAAGTACTTÄGGGGGCTCTTGTGATCAGT
1010 1030 1050 1070 1090
AGTTACCACATCGGGTCACTCTGGAGACAGACTCATCAGAGGAGGAGGCTCÄTTGATGAGGCTCTGTGTGAGACATTAATGACGCACTGT
1110 1130 1150 1170
TACTGTGTTGÄTCTCAGGÖTGTGTTGTTTÄGTGTGTGTGTTGTTTGTGTTTCTAGCTCAGAAATCTGTGAACTGACATGACGCCAGAA
1190 1210 1230 1250
GGCTACCTAGAAACAGGGACTTGGCAGGCCAAAAGCTTTCGCTGAACTCTCAGGATGGGCTGAGTACAAAGGACCACTCTGGAAAGCTGG
1270 1290 1310 1330 1350
CCGGGCTCTCÄCTGATCAGAAAGCCTGAGAGCAGAAAGGACGATGAGGTGCTGAGGACGCACTCTGACAGAGGACCATCATGAA
1370 1390 1410 1430
GTCAAAGTGGACAGAAGTTCTCGGCACTACGAGCCCTGGAGGCCGAGCTGAAGTGCATGAGGTGGGCTGTGTGACCTGAATGAT
1450 1470 1490 1510 1530
CATGAGGGCCAGACAGAGAGCCCTGCTGAGGAGCGGGAGTTCAGCTGÖCCTCAGAGGGAGCAGCTGAGAGCAACGGCCGATACAGCTGAG
1550 1570 1590 1610
GATGCTGTGCTCAGAGAGGCTGAGGCGCAGGCTCAGCTCCAAAGTCTCCAACTGTCTTCACTTGGACGAGGAGAGGCTGACCAAG
1630 1650 1670 1690 1710
GACACGCCCTCAGGCGGAGTGTGCGAGGCTCCAGTGTGGAGCAGAGAACTTGGCAGAAATCCCTGATGTGGACACAGGCTCTCT
1730 1750 1770 1790
GCCCCAGCCGACGCGCAGAGGAGAGAGAAACCGTGTGCGGAGGAACTGCTGCGAGAGTGGAGGCCAAAGCCGAGAGAGGTGAAGGCCAA
1810 1830 1850 1870 1890
GGAGGTGAGAGATCACTTTCACTACTGGAGTGTCTGGGCTCCGGCAGCGGCGACGGTGGCATGAGCAAGGCGACGAGTCCAGCTCTCT

Fig. 4 (8)

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1910 1930 1950 1970
 GAAGCGGGCGCTCAGGGGCTGCGCAGGGACTTCCGGGAGCTGCGGGCAAGGGCGTGAGCAGCTCATGTACGTCAAGGAGGATCTCAT
 1990 2010 2030 2050 2070
 CCTCCCGCACTATCACAACCTTCTACGACTTCATCGTGGCAGAAAGCCCGGGCAAGAGCGGCCCCGCTCTTCAGCTTCGAGCTGCACGACGAA
 2090 2110 2130 2150
 TGTCCGGCTGCTGAGCGATGCCACGATGGAGAAAGATGAGTCAACGCGGGCAAGGTGGTGGTCTCCGAGCTGGTACGAGAGAGAACAGCA
 2170 2190 2210 2230 2250
 CATCTTCCCTGCCAGCGCTGGGAGCCCTACACCCCGGAGAAAGTGGGACAGGTACACCATCCGGTGATGCCAAGTCCCGTCTTGGGG
 2270 2290 2310 2330
 ACCTTACTCCCTAACTATCGAAAACTAATAAATACAGAGGGTCCCGCTAAATCGGATGTGTGGTCTGTACCTGGCGCTCATCTTCGGT
 2350 2370 2390 2410 2430
 GTTTTTAATGTTCTGTGTTGTGGCTCCTTGTGTCTGTGTGAAAGGGACATGTTTTGACTAAGTGGGTGTGTCACATTAGCTTGGTG
 2450 2470 2490 2510
 GCGCAGCAGACTGGGTGTGATTTCTTGCTCAATGTCTTACTTGTGTGTGAGCAAAATCATTCGGGTCAATTGACTGCTCTTCCGCCACC
 2530 2550 2570 2590 2610
 TATACAGGAAGTTACACCCCTTCAGGCCAGCGTGAGGAGTGAGTTAATATTTGTAAACACTTGGAACTCACTCACTAAATGCGCTGCTGT
 2630 2650 2670 2690
 TTTGTGTGGGCTGGTGGTCTTTACTAAAGAAATGCCACGGGATCCATCTCTGAAATGTCAAAACAGGGGTAGACCTGCATATGTCTTGGT
 2710 2730 2750 2770 2790
 TTCAGGGTCAGTGGTGGCTGAAAGCTGGGTGACAGCTTAAAGATCGGAGCGGCTTATTTCTCTATCTTACCCAAAGCTCACATCTA
 2810 2830 2850 2870
 CATGGCAAGATCTAATTCGCCGCCCTTAAAGTTATGATATGATTAATCATTTGTGAGTGTCTTGTAAATTTTCACTTAAAGAGCTCTAAAA
 2890 2910 2930 2950 2970
 TACAGTGCATCTCTTCCACGGATTTTTTAAAGTTACCCCTTTATGTAAAGACCAAGACTTATACCTTGGATCTCTGCTGTGTCTG
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 GCGCTGAGTACTTGGCGCAGCCCAAGAACATGAATTC

Fig. 4 (B) (cont'd)

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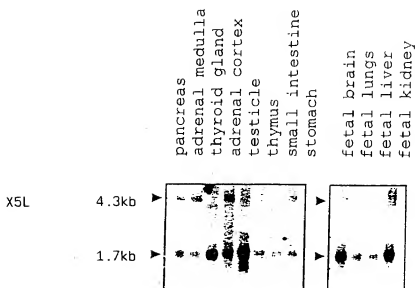


Fig. 5

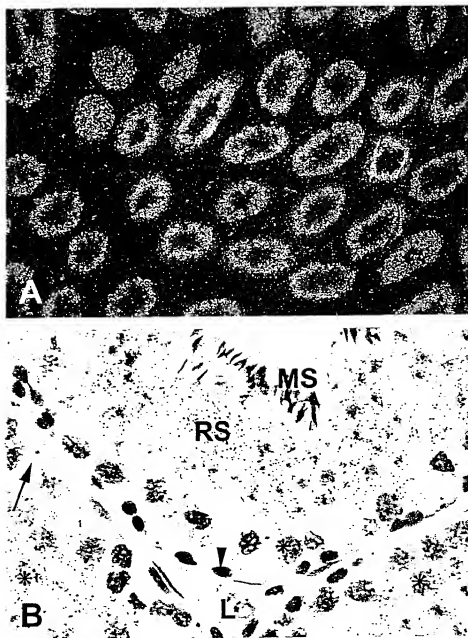


Fig. 6

K 297
PATENT APPLICATION

P330

DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION

ATTORNEY DOCKET NO. 4321-125

As a below named inventor, I hereby declare that:

My residence/post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter, which is claimed and for which a patent is sought on the invention entitled:

SPERMATOGENESIS PROTEIN

the specification of which is attached hereto unless the following box is checked:

(X) was filed on June 8, 2001 as US Application Serial No. 09/857902 or PCT International Application

Number _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119(a-d) or 365(b) of any foreign application(s) for patent or inventor(s) certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application(s) for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
Germany	198 56 882.7	10 December 1998	YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
PCT	PCT/DE99/03972	8 December 1999	YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS(patented/pending/abandoned)

POWER OF ATTORNEY.

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) listed below to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

2 Steven J. Hultquist, Reg. No. 28021

Marianne Fueller, Reg. No. 39983

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(919) 415-9350

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Inventor's Signature

Date

01.10.2001

DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION (continued)

ATTORNEY DOCKET NO. 4121-125

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5.10.2001

Inventor's Signature

Date

Full Name of Inventor: _____

Citizenship: _____

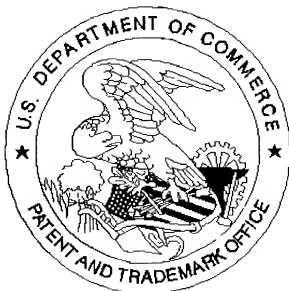
Residence: _____

Post Office Address: _____

Inventor's Signature

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